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Physical therapy interventions, other than general physical exercise interventions, in children and adolescents before, during and following treatment for cancer (Review)

Ospina PA, McComb A, Pritchard-Wiart LE, Eisenstat DD, McNeely ML

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[Intervention Review]

Physical therapy interventions, other than general physical exercise interventions, in children and adolescents before, during and following treatment for cancer

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ABSTRACT

Background

Children and adolescents diagnosed with cancer are at high risk of experiencing severe side effects from cancer treatment, many of which are amenable to physical therapy. These side effects can negatively impact a child's quality of life and ability to participate in daily activities (e.g. play and attendance at school). Researchers have evaluated physical therapy interventions in children with cancer and childhood cancer survivors. However, factors such as small sample sizes, varying intervention protocols and differences in cancer types among trials make it difficult to draw conclusions about efficacy.

Objectives

The primary aim of this review was to evaluate the efficacy of physical therapy interventions - with a specific focus on symptom relief and compensation of therapy-related side effects - on the quality of life of children and adolescents diagnosed with cancer. Participants must be between the ages of 0 and 19 years at the time of the physical therapy intervention study. The intervention may occur prior to, during or following cancer treatment. The intervention must be compared to a control group of children receiving standard care, no physical therapy intervention or a comparison intervention. We have excluded general physical exercise studies where the primary aim was to improve physical fitness through aerobic, anaerobic, resistance exercise or combined physical exercise training regimens (i.e. combined aerobic and resistance exercise regimens). We have also intended to record the occurrence of any adverse effects resulting from physical therapy interventions.

The secondary aims were to evaluate the efficacy of physical therapy on impairments of pain, peripheral neuropathy, balance, gait, functional abilities and mobility, motor function and performance, range of motion, strength and fatigue.

Search methods

We searched CENTRAL, MEDLINE, Embase, CINAHL, PEDro, ongoing trial registries, conference proceedings and the reference lists of relevant studies and reviews in March 2020. We also contacted oncology rehabilitation researchers working in paediatrics in March 2020 to identify additional studies.

Selection criteria

The review included randomised controlled trials (RCTs), cross-over trials, and controlled clinical trials (CCTs) that compared the effects of physical therapy interventions to a control group, and involved children and adolescents diagnosed with cancer between the ages of 0 and 19 years at the time of the intervention. We excluded studies examining general physical exercise interventions where the primary aim was

to improve physical fitness through aerobic exercise, resistance exercise or combined physical exercise training regimens (i.e. combined aerobic and resistance exercise regimens).

Data collection and analysis

We used standard methodological procedures expected by Cochrane.

Main results

We found no RCTs, cross-over trials or CCTs comparing the effects of physical therapy interventions with a focus on symptom relief and compensation of therapy-related side effects for children and adolescents between the ages of 0 and 19 years.

Authors' conclusions

Results demonstrate that the evidence to date is inadequate to inform clinical practice. Recommendations for future research include the need for large-scale, high-quality designs that examine: (1) paediatric populations with same cancer types; (2) similar intervention protocols; (3) long-term outcomes; (4) physical therapy interventions (e.g. electrophysical modalities and sensory interventions); and (5) outcomes commonly impaired in children with cancer (e.g. peripheral neuropathy and gait deficits).

PLAIN LANGUAGE SUMMARY

What are the effects of physical therapy interventions before, during, and after childhood cancer treatment?

Review question

We reviewed the evidence on the effects of physical therapy interventions, other than general physical exercise interventions, on the quality of life of children and adolescents diagnosed with cancer compared to a control group of children receiving standard care, no physical therapy intervention or a comparison intervention. We also reviewed the occurrence of any harms (adverse effects) resulting from the physical therapy interventions. For the purpose of this review, physical therapy interventions of interest had to have a focus on symptom relief or address therapy-related side effects (symptoms and impairments). We excluded studies examining general physical exercise interventions where the primary aim was to improve physical fitness through aerobic exercise, resistance exercise or combined physical exercise training regimens (i.e. combined aerobic and resistance exercise regimens).

Background

Children and adolescents with cancer often have side effects from cancer and its treatments. These side effects can negatively impact a child's quality of life and ability to participate in daily activities such as play. Researchers have carried out studies that examine physical therapy interventions in children with cancer. However, the benefits of physical therapy are unclear.

Study characteristics

The evidence is current to March 2020. We did not identify any eligible studies.

Key results

We did not identify any studies that examined on the effects of physical therapy interventions on the quality of life of children and adolescents diagnosed with cancer, compared to a control group of children receiving standard care, no physical therapy intervention or a comparison intervention. Thus, no conclusions can be made. Our results show that further research is needed examining the effects of physical therapy interventions in children and adolescents with cancer.

SUMMARY OF FINDINGS

Summary of findings 1. Physical Therapy compared to standard care, no physical therapy intervention or a comparison intervention in children and adolescents before, during and following cancer treatment

Physical therapy compared to usual care in children and adolescents before, during and following cancer treatment

Patient or population: children and adolescents before, during and following cancer treatment
Setting: any
Intervention: physical therapy
Comparison: standard care, no physical therapy intervention or a comparison intervention.

Outcomes	Comments
Quality of Life	No studies included
Fatigue	No studies included
Pain	No studies included
Balance	No studies included
Range of motion	No studies included
Strength	No studies included
Adverse events	No studies included

BACKGROUND

Description of the condition

It is estimated that, globally, around 300,000 children and adolescents between the ages of 0 and 19 years will be diagnosed with cancer each year (Kids Cancer Care 2020; WHO 2020). Over 175,000 (70%) will be children under the age of 15 years (Ward 2014). Progress in cancer treatments has resulted in improved survival rates for children and adolescents with cancer, now approaching or exceeding 80% for five-year post-diagnosis survival (Gatta 2014; Noone 2018). Thus, there is an increased awareness of the need for survivorship care plans, including medical follow-up and surveillance for long-term effects of cancer treatment (Buckner 2014; CCS 2020; Robison 2009).

Two-thirds of children who have been diagnosed with cancer will also develop at least one chronic or long-term side effect after the cancer treatment (CCS 2020; Skinner 2012). Long-term and late effects are expected health complications resulting from the cancer or cancer therapy (chemotherapy, radiation therapy, surgery and stem cell transplant), that never resolve or emerge months or years following treatment completion, and impact overall health and quality of life (Green 2012). These effects include impairments such as pain, fatigue, weakness, peripheral neuropathy, limitations in range of motion, and deficits in balance and gait (Baggott 2009; Beulertz 2016b; Gilchrist 2016; Gilchrist 2018; Hartman 2008; Ness 2013; Robison 2009; Skinner 2012; Van Cleve 2012). All of these may negatively affect a child's overall function, quality of life and ability to participate in age-appropriate activities including play (Moody 2006; Pruitt 2009).

Cancer treatments can negatively impact the major body systems including musculoskeletal, cardiorespiratory, and neurological systems (Pruitt 2009). The risk of long-term side effects are dependent on the tumour type and tumour-related factors (e.g. location within the body and extent of the cancer); the type of cancer treatment administered (e.g. type of surgery, chemotherapy type and dosage, radiation therapy type, location and dosage); as well as patient-related factors (e.g. the child's gender, age, overall health pre-cancer diagnosis and developmental stage at time of diagnosis) (Pruitt 2009; NCI 2020). The focus of this review was on the outcomes associated with physical interventions for musculoskeletal and neurological effects of cancer and cancer treatment.

Musculoskeletal System

Specific long-term effects from cancer treatment on the musculoskeletal system include effects on muscle and soft tissues (myopathies including proximal muscle weakness, soft tissue contracture and radiation fibrosis syndrome), as well as effects on bone resulting in scoliosis or kyphosis, limb length discrepancies and osteoporosis (NCI 2020; Pruitt 2009). The impact of surgery such as amputation and limb-salvage intervention may result in chronic pain, gait and balance dysfunction, and impact overall activity (Krivitzky 2015; Pruitt 2009). Effects involving the musculoskeletal system are more likely to occur in cancers such as acute lymphoblastic leukaemia, osteosarcoma, and brain and spinal cord tumours; and in those children who have undergone a stem cell transplant (NCI 2020; Pruitt 2009).

Neurological System

Specific long-term effects involving the neurological system include motor and sensory deficits (loss of fine motor skills, impairments in coordination and balance, movement disorders and peripheral nerve damage in the hands and feet) (Krivitzky 2015; NCI 2020; Pruitt 2009). Chronic peripheral neuropathy, a condition that may result from the use of neurotoxic agents such as vincristine and cisplatin, is a common long-term effect experienced by both childhood and especially adult survivors (Kandula 2016; Pruitt 2009; Wickham 2007).

Description of the intervention

Focused physical therapy interventions may help children with the late and long-term physical effects resulting from cancer treatments, particularly prolonged cancer treatments (Stubblefield 2013). Physical therapists aim to restore and optimise function, mobility and quality of life of individuals of all ages (Punzalan 2009). In oncology rehabilitation, physical therapists work with individuals to manage musculoskeletal and neuromuscular impairments (Punzalan 2009). Rehabilitation for cancer patients include treatments to address acute, late and long-term effects, as well as those associated with palliative care (Punzalan 2009), with the ultimate aim of improving quality of life.

Physical therapists perform assessments to determine physical function, joint mobility, muscle strength and flexibility. Findings of the assessment are used to inform an appropriate, tailored intervention for the child (Punzalan 2009). Physical therapy for children with cancer aims to regain function through interventions to reduce pain in soft tissues (muscles, tendons and ligaments), increase muscle strength, improve soft tissue and joint flexibility, range of motion and functional mobility. Treatment can be delivered before (prehabilitation), during and after cancer treatment completion (rehabilitation) (Krivitzky 2015). Prehabilitation services include interventions that are administered between the time of diagnosis and cancer treatment initiation. Prehabilitation interventions may be prescribed to enhance a child's physical functioning and general health status to enable improved tolerance to cancer treatments, overall outcomes and recovery from the prospective cancer treatment. Rehabilitation services delivered during or following cancer treatment are defined as services to decrease adverse effects of treatment and to enhance recovery of functional abilities. Importantly, focused and timely physical therapy intervention may help to prevent the development of late effects and attenuate the severity of long-term effects (Krivitzky 2015).

The interventions considered in this review included physical therapy techniques such as manual therapy, therapeutic range of motion and strengthening exercises for a joint or muscle region, balance retraining, gait re-education and electrophysical modalities provided with the aim of addressing impairments related to cancer treatment to ultimately improve quality of life. For this review, physical therapy could have been delivered as prehabilitation or rehabilitation interventions. The children and adolescents participating in the included studies needed to have been between 0 and 19 years old at the time of receipt of the physical therapy intervention in the studies.

Why it is important to do this review

To date, the majority of research trials in cancer rehabilitation have involved adult cancer survivors. Researchers have reported positive results from physical therapy interventions, primarily in the area of breast cancer (Cho 2016; De Groef 2015; McNeely 2010; Nilsen 2015; Pergolotti 2015).

Impairment-based cancer rehabilitation for children and adolescents with cancer is a growing area of research and clinical practice. Researchers have evaluated physical therapy interventions in children with cancer and childhood cancer survivors. However, factors such as small sample sizes, varying intervention protocols and differences in cancer types among trials make it difficult to draw conclusions about efficacy.

A recent Cochrane Review examined the effects of general exercise training interventions for children and adolescents with cancer (Braam 2016). The review included six studies involving 171 participants, all of whom were being treated for acute lymphoblastic leukaemia. Preliminary findings support benefit from general physical exercise training for body composition, flexibility and cardiorespiratory fitness. To date, however, no systematic reviews have been performed examining the benefits of physical therapy interventions for specific impairments related to cancer treatment. Thus, the main distinctions between this review and that of Braam 2016 were: (1) the type of intervention (physical therapy versus general physical exercise); and (2) the focus of the intervention (amelioration of specific iatrogenic impairments versus physical fitness).

OBJECTIVES

Primary objective

To evaluate the efficacy of physical therapy interventions - with a specific focus on symptom relief and compensation of therapy-related side effects - on the quality of life of children and adolescents who have been diagnosed with cancer. Participants must be between the ages of 0 and 19 years at the time of the physical therapy intervention study. The intervention may occur prior to, during or following cancer treatment. The intervention must be compared to a control group of children receiving standard care, no physical therapy intervention or a comparison intervention. We have excluded general physical exercise studies where the primary aim was to improve physical fitness through aerobic, anaerobic, resistance exercise or combined physical exercise training regimens (i.e. combined aerobic and resistance exercise regimens). We have also intended to record the occurrence of any adverse effects resulting from physical therapy interventions.

Secondary objectives

To evaluate the efficacy of physical therapy interventions on pain, peripheral neuropathy, balance, gait, functional abilities and mobility, motor function and performance, range of motion, strength and fatigue.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs), cross-over trials (when data were available prior to the cross-over), and controlled clinical trials (CCTs) examining the effects of physical therapy interventions for children and adolescents between the ages of 0 and 19 years.

Types of participants

Children and adolescents aged 0 to 19 years at the time of the physical therapy intervention. All childhood cancer types were eligible for inclusion in the review. We considered studies that also included adults (20 years old or more) with cancer only if the results of the subgroup of children with cancer (0 to 19 years of age) were available or reported separately.

Types of interventions

We included studies comparing physical therapy interventions (such as manual therapy techniques, therapeutic range of motion and strengthening for a specific joint or impaired body region, balance and gait retraining), and electrophysical modalities to address a specific symptom (e.g. pain), impairment (e.g. gait dysfunction) or body region (e.g. shoulder). For the purpose of this review, physical therapy interventions of interest had to have a focus on symptom relief and compensation of therapy-related side effects. The intervention may have been delivered before (prehabilitation), during or following cancer treatment. The intervention had to be compared to a control group receiving standard care, no intervention or a comparison intervention (assuming the effect of the physical therapy intervention can be isolated).

The physical therapy intervention had to be delivered or supervised by a physical therapist or healthcare professional (e.g. nurse or occupational therapist). The programme could have been offered as an individualised treatment or a group intervention, and performed in any setting or location (e.g. hospital, outpatient hospital or physical therapy clinic, home, or elsewhere). The duration of the physical therapy intervention period had to be at least four weeks. The time spent per physical therapy session had to be reported or sufficiently described, and delivery of the intervention had to last at least 15 minutes (Hanson 2015; Ospina 2019).

Exclusion criteria

- Studies where the primary focus of the intervention was aerobic capacity or general physical fitness alone.
- Studies where the intervention comprised a general exercise or physical activity prescription, described in terms of frequency, intensity, type and time.

Types of outcome measures

Primary and secondary outcomes listed below were not used as criteria for including studies, but rather as a list of outcomes of interest within the included studies.

Primary outcomes

The primary outcomes of this review were quality of life and adverse events.

- Quality of life: measured by scales such as the Pediatric Quality of Life Inventory (PedsQL), Pediatric Quality of Life (PedsQL Core), Child Health Questionnaire (CHQ), and DISABKIDS or other validated questionnaires.
- Adverse events related to the physical therapy intervention such as falls, fractures, soft tissue injuries, or any worsening of impairments (e.g. pain) requiring withdrawal from the study.

Secondary outcomes

Secondary outcomes of the review are as follows.

- Pain measured by Visual Analog Scale (VAS), or other valid instruments.
- Peripheral neuropathy measured by a validated scale such as the Pediatric Modified Total Peripheral Neuropathy Score (ped-mTNS), Total Neuropathy Score-Pediatric Vincristine (TNS-PV), or Total Neuropathy Score (TNS).
- Balance assessed by a validated scale such as the Bruininks Osteretsky Test of Motor Proficiency (BOTMP) Balance Subtest, Bruininks Osteretsky Test of Motor Proficiency Second Edition (BOT-2) Balance Subtest, Pediatric Berg Balance Scale (BBS), Movement Assessment Battery for Children (Movement ABC-2), the Flamingo Balance Test or equivalent.
- Motor development and performance measured by a validated scale such as Bruininks Osteretsky Test of Motor Proficiency (BOTMP), Bruininks Osteretsky Test of Motor Proficiency Second Edition (BOT-2), Alberta Infant Motor Scale (AIMS), Movement Assessment Battery for Children (Movement ABC-2), Peabody Developmental Motor Scales (PDMS-2), Miller Function and Participation Scales (MFUN-PS), Gross Motor Function Measure (GMFM), or another valid instrument.
- Functional abilities and mobility assessed by a validated scale such as the Functional Mobility Assessment (FMA) tool, Timed Up and Down Stairs (TUDS), Timed Up and Go (TUG), Functional Independence Measure for Children (WeeFIM), Pediatric Evaluation of Disability Inventory (PEDI), Vineland Adaptive Behaviour Scale, or another valid instrument.
- Gait assessed descriptively or by use of a computerised or electronic gait analysis.
- Fatigue assessed by a validated scale such as the PedsQL Multidimensional Fatigue Scale, Childhood Cancer Fatigue Scale (CCFS), or the Fatigue Scale for a child (FS-C), the same scale for adolescents (FS-A), and for parents (FS-P), or equivalent valid instrument.
- Range of motion measured by goniometry, or another valid instrument.
- Strength assessed with a hand-held dynamometer, use of a Biodex/Cybex, spring scale, lateral step-up test, sit-to-stand test, up-and-down stairs test, minimum chair height test, incremental shuttle walking test, or another valid instrument.

Search methods for identification of studies

In 2018, Cochrane Childhood Cancer ran the searches in CENTRAL, MEDLINE and Embase. In 2020, the review authors ran all searches (CENTRAL, MEDLINE, Embase, CINAHL, PEDro, ongoing trial registries, conference proceedings, reference lists of relevant articles, and personal communication with researchers). No language restrictions were applied.

Electronic searches

We searched the following electronic databases: the Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library — we used the latest issue; MEDLINE Ovid (from 1946 to 15 March 2020); Embase Ovid (from 1947 to 15 March 2020); CINAHL/EBSCO (1937 to 15 March 2020); and Physiotherapy Evidence Database PEDro (from 1929 to 15 March 2020) (www.pedro.org.au). We modified electronic searches from the recommended Cochrane Childhood Cancer methods used in reviews (Kremer 2016).

The search strategies for the different electronic databases (using a combination of controlled vocabulary and text words) are shown in the appendices (Appendix 1; Appendix 2; Appendix 3; Appendix 4; Appendix 5).

Searching other resources

Bibliographic searching

We searched for trials not registered in CENTRAL, MEDLINE, Embase, CINAHL and PEDro, either published or unpublished, by searching the reference lists of relevant articles and review articles. We searched the five latest editions (2015-2019) of conference proceedings of the International Society for Paediatric Oncology (SIOP), the American Society of Clinical Oncology (ASCO), the American Society of Pediatric Hematology/Oncology (ASPHO), and the Multinational Association for Supportive Care in Cancer (MASCC). We scanned the ISRCTN Registry (www.isrctn.com), the National Institutes of Health (NIH) Register (www.clinicaltrials.gov), and the World Health Organization portal (http://apps.who.int./trialsearch) for ongoing trials on 14 March 2020.

The search strategies for other resources are shown in the appendices (Appendix 6; Appendix 7).

Personal communication

We contacted oncology rehabilitation researchers working in paediatrics to verify details of any outstanding clinical trials and any relevant unpublished data or study information.

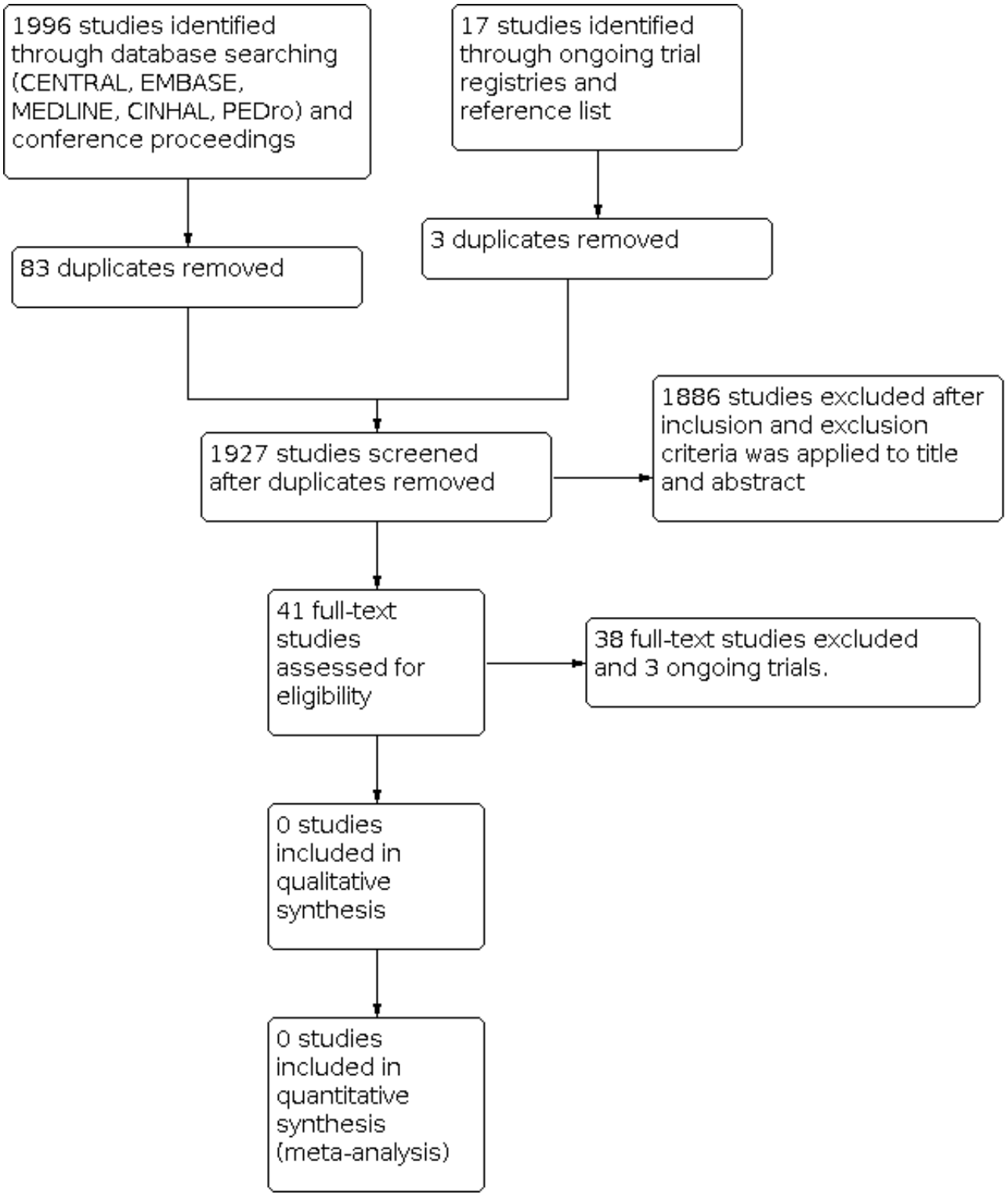
Data collection and analysis

Selection of studies

Two authors independently undertook identification of studies meeting the inclusion criteria. In most cases, we resolved discrepancies between authors by consensus. The authors resolved disagreements through discussion, or if necessary, by involving a third review author to reach consensus. We obtained any study seemingly meeting the inclusion criteria on the grounds of the title, abstract, or both, in full for closer inspection. We clearly stated details of reasons for exclusion of any study considered for review. We would have noted duplicate publications of the same study, and the study would have been counted only once.

We provided a flow diagram for the selection of studies in our review (Figure 1).

Figure 1. Study flow diagram



Data extraction and management

Two review authors would have extracted the characteristics for each included trial using a data extraction form. If disagreements had arisen and were not resolved by consensus, a third review author would have resolved the discrepancies. In case of missing data or relevant information, we would have contacted study authors.

Should we have had more than one publication for a study, we would have used the primary publication and referenced the other publication, if used, for supplementary information.

Items that we would have included on the data extraction form are reported in the protocol of this review (Ospina 2018).

Assessment of risk of bias in included studies

If studies had met our eligibility criteria, two review authors would have independently assessed risk of bias in the RCTs, cross-over trials and CCTs, rating each risk of bias item as 'low', 'unclear' or 'high' risk of bias. We would have used the 'risk of bias' criteria as described in the module of Cochrane Childhood Cancer (Kremer 2016), and based on recommendations in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). The two review authors would have resolved any disagreements through discussion, or if necessary, by involving a third review author to reach consensus. Further details can be found in the protocol of this review (Ospina 2018).

Measures of treatment effect

If studies had met our eligibility criteria, we would have analyzed continuous data (QoL, adverse events, fatigue, pain, gait, peripheral neuropathy, balance, range of motion, strength) as mean differences either weighted or standardised using a random-effects model. We would use difference in means (MD) for continuous variables when data are provided using the same units, measurement methods or outcome measure. We would use the standardised mean difference (SMD) for continuous variables when trials report results using different measurement units, measurement methods or outcome measures. We would analyze dichotomous outcomes (e.g. adverse event rates, outcomes reported as dichotomous variables) using risk ratio (RR). All results would be presented with corresponding 95% confidence intervals (CIs).

Unit of analysis issues

If studies had met our eligibility criteria, the only unit of analysis issue we anticipated is with cross-over designs, in which we would use only first-cycle data (prior to cross-over).

Dealing with missing data

If studies had met our eligibility criteria, when information relevant to study selection, data extraction or assessment of risk of bias was missing, we would attempt to contact the authors to obtain the missing data. When applicable, we would extract data by allocated intervention, irrespective of compliance with the allocated intervention, to allow an intention-to-treat analysis. We would state if this is not possible and will perform an 'as treated' analysis.

Assessment of heterogeneity

If studies had met our eligibility criteria, we would assess heterogeneity by visual inspection of the forest plots and by the use of the statistical test for heterogeneity I^2 statistic (Higgins 2011). I^2 values ranging from 0% (homogeneity) to 100% (heterogeneity) will be calculated to quantify variability in study effect. An I^2 value greater than 50% would be considered the cutpoint for significant heterogeneity (Higgins 2011). Where possible, subgroup analyses would be performed to explore and explain heterogeneity among studies.

Assessment of reporting biases

In addition to the evaluation of reporting bias as described in the Assessment of risk of bias in included studiessection, we planned to assess reporting bias by constructing a funnel plot if there are a sufficient number of included studies (at least 10 studies included in a meta-analysis), otherwise the power of the tests is too low to distinguish chance from real asymmetry (Higgins 2011).

To minimise the effect of publication bias, we searched the grey literature and contacted authors of trials.

Data synthesis

We did not identify any eligible studies. As a result, data analyses could not be performed. If studies had met our eligibility criteria, we would enter data of the included studies into Review Manager 5 software (Review Manager 2014) and undertake analyses according to the guidelines of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

We would pool the results of studies, (1) if there are at least three studies with the same outcome measure (or measurement) for the given primary or secondary outcome; and (2) if appropriate, after consideration of heterogeneity between the trials. We will pool outcomes when sufficient data are available in the papers or from the trialists' data sets using the random-effects model. We will describe outcomes that we cannot pool in narrative form in the Results section. We would create a 'Summary of findings' table, including post-intervention results as well as short-term follow-up results (3 to 6 months after the intervention completion) and long-term follow-up results (1 year or more after the intervention completion).

In a multi-arm study we would include the intervention groups as separate comparisons if each arm meets the criteria for inclusion, and would split the 'shared' control/comparison group for analyses. We would note all the intervention groups in the table of 'Characteristics of the included studies'. However, we would only describe and analyse the intervention groups relevant to the review (Higgins 2011).

Subgroup analysis and investigation of heterogeneity

If studies had met our eligibility criteria, we would have analyzed, a priori subgroup analyses would include examining the pooled effect estimate by the type of physical therapy intervention, the timing of the intervention (i.e. prior to, during, or following cancer treatment), and cancer type.

Where possible, we would perform subgroup analyses to assess if the observed effect of an intervention is consistent across participants based on subgroups of (1) age of the participant (continuous co-variate) and (2) the location of the physical therapy intervention (inpatient hospital, outpatient clinic or home), and (3) by study design (RCT, CCT, cross-over).

Sensitivity analysis

If studies had met our eligibility criteria, for any outcomes for which pooling was possible we would perform sensitivity analyses for 'Risk of bias' criteria separately. We would exclude studies with a high risk of bias and unclear risk of bias in the sensitivity analyses, and compare the results of studies with a low risk of bias with the results of all available studies. Sensitivity analyses would only be

done when there remain at least two studies with a low risk of bias in the analyses

Summary of findings and assessment of the certainty of the evidence

For each comparison we prepared a 'Summary of findings' table using the GRADE profiler software (Guyatt 2008), in which we presented the following outcomes: QoL, fatigue, pain, balance, range of motion, strength, adverse events.

We did not identify any eligible studies. As a result, GRADE assessments could not be performed. If studies had met our eligibility criteria, For each outcome two review authors would independently assess the quality of the evidence by using the five GRADE considerations, i.e. study limitations, inconsistency, indirectness, imprecision and publication bias, as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

RESULTS

Description of studies

Results of the search

We conducted searches of CENTRAL, MEDLINE, Embase, CINAHL, PEDro, ongoing trial registries, conference proceedings (SIOP, ASCO, ASPHO, and MASCC), and reference lists of relevant studies and reviews. We also contacted oncology rehabilitation researchers working in paediatrics for additional studies. These searches resulted in the retrieval of 2013 references (Figure 1).

After removal of duplicates, the search yielded 1927 potentially eligible articles (Figure 1). After initial screening of titles and abstracts, we excluded 1886 references as they did not meet eligibility criteria. We obtained, read and assessed for eligibility the full-text versions of 41 studies. Thirty-eight of these studies did not meet eligibility criteria (refer to Characteristics of excluded studies), and we excluded three studies as they were protocols or reported preliminary results of ongoing trials (refer to Characteristics of ongoing studies). No studies were eligible for the review (refer to Characteristics of included studies).

Included studies

We identified no trials that matched our inclusion cirteria.

Excluded studies

Reasons for exclusions can be found in Characteristics of excluded studies.

Risk of bias in included studies

We found no RCTs, cross-over trials or CCTs comparing the effects of physical therapy interventions, with a focus on symptom relief and compensation of therapy-related side effects, for children and adolescents between the ages of 0 and 19 years, and risk of bias assessment is thus not applicable.

Effects of interventions

See: **Summary of findings 1** Physical Therapy compared to standard care, no physical therapy intervention or a comparison intervention in children and adolescents before, during and following cancer treatment

We found no RCTs, cross-over trials or CCTs comparing the effects of physical therapy interventions for children and adolescents between the ages of 0 and 19 years, and thus the effects of physical therapy interventions on the quality of life of children and adolescents diagnosed with cancer remain unclear.

DISCUSSION

Summary of main results

A growing number of studies have investigated the effects of physical therapy in adults with cancer (Cho 2016; Cormie 2017; De Groef 2015; McNeely 2010; Nilsen 2015; Pergolotti 2015). Conversely, literature examining the effects of physical therapy in childhood cancer is just beginning to emerge. Unfortunately, the vast majority of the research examining the effects of physical therapy in childhood cancer comprises lower-quality study designs (e.g. single-subject designs, case-control studies) not eligible for this review (Ospina 2019). No eligible studies could be included.

Although no studies met our eligibility criteria, it is promising that further research in paediatric oncology physical therapy is underway. Our review identified three ongoing clinical trials that might be eligible for this review upon completion (Tanner 2016; Tanriverdi 2017; Xipell 2019).

Overall completeness and applicability of evidence

As demonstrated in this review, there is a paucity of high-quality research evidence from studies examining physical therapy interventions with a focus on symptom relief and compensation of therapy-related side effects in children and adolescents with cancer. Of note, chemotherapy-induced peripheral neuropathy (CIPN) is one of the most common side effects in children undergoing cancer treatment, causing debilitating consequences such as balance issues, gait impairments, muscle weakness and sensory impairments. Despite the lack of research examining the effects of physical therapy for commonly occurring side effects in childhood cancer, it is promising that clinical trials are currently in progress (Weiner 2019; Wickham 2007).

Quality of the evidence

We identified no eligible studies for inclusion.

Potential biases in the review process

We developed comprehensive search strategies to cover the main databases relevant to our research question, including: CENTRAL, MEDLINE, Embase, CINAHL and PEDro. It is possible that we missed studies. However, our search results retrieved repeats of many of the same studies across databases, suggesting that a comprehensive search was performed. Also, we searched reference lists and conference proceedings to minimise the risk of missing relevant literature. Finally, we excluded studies from this review - even though many incorporated a physical therapy intervention - due to an overlap with the review of Braam 2016.

Agreements and disagreements with other studies or reviews

To our knowledge, this is the first systematic review specifically focused on physical therapy interventions, other than general physical exercise interventions, in children and adolescents before, during and following treatment for cancer. Other reviews have

been conducted exploring general exercise interventions and non-pharmacological interventions in childhood cancer survivors. Braam 2016 published an updated version of their previous systematic review (Braam 2013), examining the effects of physical exercise in childhood cancer. Braam 2016 included six studies (n = 171), of which five were RCTs and one was a controlled clinical trial. None of the studies included in their review - De Macedo 2010, Hartman 2009, Marchese 2004, Moyer-Mileur 2009, Tanir 2013, and Yeh 2011 - met the eligibility criteria of this review either because (1) physical activity was the primary interest of these studies, or (2) the effect of the physical therapy intervention could not be isolated from the physical activity or exercise intervention. Braam 2016 concluded that overall findings of the benefits of physical exercise interventions were not convincing possibly due to the small number of participants and lack of high quality evidence, but it can also be that this type of intervention is not as effective as in adult cancer patients. However, Braam and colleagues did identify positive intervention effects for body composition, flexibility, cardiorespiratory fitness, muscle strength and health-related quality of life (cancer-related items). They also reported that the quality of the evidence was low, suggesting that further research is needed using larger-scale studies.

Wacker 2017 conducted a systematic review on nonsurgical, nonpharmacologic, rehabilitation interventions on physical impairments and functional mobility limitations for children and adolescents undergoing treatment for non-central nervous system cancers. They included a total of 22 studies in their review. No restrictions on study design were applied; thus, uncontrolled studies and case-control studies were included. Their findings comprised a general overview of interventions in the field, but did not consider quality and risk of bias. The authors identified that the majority of the studies were focused on increasing physical activity, with few studies evaluating physiotherapeutic interventions for other outcomes.

A recent systematic review by Morales 2018 investigated RCTs that examined the effects of exercise training on physical capacity-related endpoints, survival, disease relapse and adverse effects in children after cancer diagnosis. They included a total of eight studies (n = 283) in their review. Results demonstrated that exercise training during childhood cancer treatment significantly improved Timed Up and Down Stairs (TUDS) scores (SMD -0.73, P < 0.001). These findings, however, were based on pooling of data that also included exercise-based studies not eligible for inclusion in our review.

AUTHORS' CONCLUSIONS

Implications for practice

Results obtained in this review demonstrate that research evidence is lacking to inform clinical practice. Since research data are lacking, physical therapists should consider other approaches to exchange expertise, such as workshops, meetings, online platforms, interviews and Delphi techniques.

Implications for research

To date, there are no data to support the safety or efficacy of physical therapy interventions for children with cancer. Many studies have focused on general exercise interventions to improve physical fitness. Recommendations for future research include the need for large-scale, multi-centre, high-quality research designs (e.g. RCTs and CCTs) with adequate power to analyse results. These studies should: (1) include paediatric populations comprising the same cancer type; (2) adopt similar intervention protocols; (3) deliver physical therapy interventions including, but not limited to, gait retraining, use of electrophysical modalities, manual therapy and sensory interventions; (4) assess outcomes such as chemotherapy-induced peripheral neuropathy (CIPN), cancer-related fatigue, balance and gait, which are commonly impaired in children with cancer; and (5) include long-term follow-up assessments of physical therapy interventions.

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CHARACTERISTICS OF STUDIES

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Beulertz 2016a	Exploratory prospective study that included a general exercise intervention conducted by a sports therapist.
Braam 2010	Physical fitness is the primary objective of the study.
Braam 2018	A combined intervention where the effect of the physical therapy intervention could not be isolated from the physical activity-based intervention.
Casanova-Garcia 2015	This is a research proposal and preliminary data were presented as case series.
Corr 2017	A combined intervention where the effect of the physical therapy intervention could not be isolated from the physical activity-based intervention.
Cox 2018	The effects of the nursing motivation-based intervention are not isolated from the physical therapy intervention.
Cunningham 1986	Sample combined adults and children.
Däggelmann 2017	Comparison group included healthy controls.
De Macedo 2010	Respiratory rehabilitation intervention, did not meet criteria of our physical therapy interventions of interest.
Fiuza-Luces 2017	Physical activity-based intervention. Both groups received physical therapy only as needed.
Gohar 2011	Uncontrolled study.

Study	Reason for exclusion
Hartman 2009	A combined intervention where the effect of the physical therapy intervention could not be isolated from the physical activity-based intervention.
Kim 2019	Uncontrolled study. Physical activity-based intervention.
Lam 2018	Behaviour change intervention.
Manchola-Gonzalez 2019	Physical fitness is the focus of the study. A combined intervention where the effect of the physical therapy intervention could not be isolated from the physical activity-based intervention.
Marchese 2004	A combined intervention where the effect of the physical therapy intervention could not be isolated from the physical activity-based intervention.
Morales 2019	Physical exercise intervention.
Moyer-Mileur 2009	Physical fitness is the primary objective of the study.
Müller 2014	Study outcomes were primarily bone mass and physical activity.
Müller 2016	Uncontrolled study.
Müller 2017	Uncontrolled study.
Ouyang 2019	Physical activity-based intervention.
Rosenhagen 2011	Case-control study. Evaluates the integration of sports activity.
Sabel 2016	Physical activity-based intervention.
San Juan 2008	Physical exercise intervention. Used healthy control group.
Speyer 2010	Physical activity-based intervention.
Tanir 2013	Physical exercise intervention.
Tanner 2015	Uncontrolled study.
Tanner 2017	Uncontrolled study.
Tanner 2018	A combined intervention where the effect of the physical therapy intervention could not be isolated from the physical activity-based intervention.
Tomasello 2018	Uncontrolled study.
Van Dijk-Lokkart 2016	Physical exercise intervention.
Wallek 2018	Primarily physical exercise intervention. Also, it seems that this paper presents secondary analysis of a trial that may already be published or is in process.
Winter 2013	Prospective, cohort study focused on physical activity.
Wurz 2019	Physical activity-based intervention.
Yeh 2011	Aerobic exercise intervention.

Characteristics of ongoing studies *[ordered by study ID]*

Tanner 2016

Study name	Impact of an Orthotic Intervention in Children with Peripheral Neuropathy (IOPN)
Methods	Type of study: interventional Setting: Children's Hospitals and Clinics of Minnesota Department: Developmental and Rehabilitation Services Randomisation: randomisation through parallel assignment with each group receiving a different type of orthotic Stratification: not mentioned Timing: children undergoing treatment Study duration: 8 weeks End point measurements: measured at baseline and after study completion (8 weeks) Trial register: NCT03655587
Participants	N = 50 (estimated) Diagnosis: children with a cancer diagnosis Inclusion criteria: children aged 5 to 14 years old demonstrating neuropathy (PedmTNS score > 4), with a normalised step length more than 1 standard deviation below the mean for their age and ankle dorsiflexion passive range < 10 degrees Age at start of study: 5 to 14 years old Exclusion criteria: children with lower extremity sarcomas, children with central nervous system tumours, children with neurological, developmental or genetic disorders, children with osteonecrosis, children with less than antigravity dorsiflexion strength and children with neuroblastomas
Interventions	The subjects were randomised between an 8-week ankle foot orthosis (AFO) or ankle resting night spring (RNS) intervention. The orthotic was fitted with a small temperature sensor that collected data for wearing time of the brace. The solid foot ankle orthotic is made to fit the contour of the patient's foot, ankle and lower leg. The two pull solid ankle AFO is fabricated from a rigid polypropylene outer boot and a more flexible silicone inner boot. It is commonly used in rehabilitation to improve gait in paediatric and adult populations. A certified orthotist fabricated the device. The resting night splint group received an off-the-shelf device that provides static sagittal plane dorsiflexion. The RNS was worn nocturnally to provide maximal stretch/length to the gastrocnemius and soleus to maintain or increase dorsiflexion range of motion (ROM) and/or to prevent further regressions in ankle range.
Outcomes	Primary outcomes: Step length: 'GAITRite' analysis system Secondary outcomes: Ankle range of motion: passive and active ankle dorsiflexion measured by goniometry Ankle strength: ankle dorsiflexion and plantar flexion strength measured by dynamometer Gait capacity: Six-minute walk test (6MWT) distance Foot posture: foot posture index
Starting date	20 September 2016
Contact information	Lynn Tanner, telephone: 612-813-6274
Notes	Estimated study completion 30 June 2021. On 23 June 2020, no full-text publication was available.

Tanriverdi 2017

Study name	The Effect of Virtual Reality Exercises on Balance in Children with Brain Tumours

Tanriverdi 2017 *(Continued)*

Methods	Type of study: interventional Setting: Bezmialem Vakif University Department: Physiotherapy and Rehabilitation Randomisation: randomised through parallel assignment Stratification: not mentioned Timing: after surgical intervention Study duration: 8 weeks End point measurements: at baseline and at 8 weeks (study completion) Trial register: NCT03142087
Participants	N = 30 Diagnosis: brain tumour Inclusion criteria: children aged 6 to 18 years old with the diagnosis of a brain tumour Age at start of study: 6 to 18 years old Exclusion criteria: children with conditions with exercise, children with neurological or musculoskeletal disorders
Interventions	The study group included in the Nintendo Wii Fit Plus Balance Game exercise program were under the supervision of a physiotherapist for 2 days per week for 8 weeks. The virtual reality exercises were performed on the Nintendo Wii Fit Plus Game Console. Sessions consisted of warm up exercises for 5 to 10 minutes, followed by games (soccer heading, ski jumping, slalom, etc.) for 30 to 40 minutes, and cool down exercises for 5 minutes. The control group was taken to a physiotherapy/rehabilitation exercise program under the supervision of a physiotherapist for 2 days a week, 1 hour a day. The control group program comprised of warm up exercises for 5 to 10 minutes, followed by balance and weight bearing exercises for 30 to 40 minutes and a cool down of 5 minutes.
Outcomes	Physical function: Anthropometric evaluations, muscle strength measurement, pain visual analogue scale, observational walking analysis, balanced paediatric functional range test, Timed Up and Go, one foot standing test, Nintendo Wii Fit Plus Balance Assessment, Functional capacity 2 minutes, fatigue with PedsQL Multidimensional Fatigue Scale, daily life activities with WeeFIM.
Starting date	21 March 2017
Contact information	Müberra Tanrıverdi
Notes	Study completed in January 2018. On 23 June 2020, no full-text publication was available.

Xipell 2019

Study name	Horse Assisted Rehabilitation Postoncologic Treatment in Children and Adolescents: Physical and Psychological Effects
Methods	Type of study: interventional Setting: Bezmialem Vakif University Department: Physiotherapy and Rehabilitation Randomisation: Randomised through parallel assignment Stratification: not mentioned Timing: over 6 months after surgical intervention Study duration: 6 months End point measurements: baseline, 6-week, 12-week, and 25-week (study completion) Trial register: NCT04070131
Participants	N = 30 Diagnosis: cancer with affectation of the central nervous system Inclusion criteria: children aged 4 to 18 years old with the diagnosis of a brain tumour; with or without motor, functional and/or cognitive deficits or neurological disorders due to their basic prob-

Xipell 2019 *(Continued)*	
	lem or as a consequence of the therapeutic procedures, with any degree of disability; more than 6 months after receiving the discharge of oncology (chemotherapy or radiotherapy). Exclusion criteria: children with Immunodepression, hypotonia with severe pelvic instability that does not allow seating on the horse safely, weight greater than 80 kg, and phobia of horses.
Interventions	Control group: standard follow-up Intervention group: horse-assisted rehabilitation (1 hr per week) and session of hippotherapy.
Outcomes	**Primary outcome measures** Self-reported quality of life changes (Pediatric Quality of Life Inventory - Child Self-Report (PedsQL-C)) **Secondary outcome measures** Parent-proxy-reported quality of life changes (Pediatric Quality of Life Inventory - Parent-Proxy Report (PedsQL-PC)) General health status changes (Barcelona General Health Status Questionnaire 2000) Anxiety changes (State Trait Anxiety Inventory for children (STAI-CH)) Depression changes (Childhood Depression Inventory (CDI)) Behavior changes ((Behavior Assessment System for Children - Parent Rating Scale (BASC-PRS)) Self-reported physical function changes (PedsQL-C (subscale Health and Activities)) Parent-reported physical function changes (PedsQL-PC (subscale Physical Functioning)) Self-reported emotional function changes ((PedsQL-C (subscale Feelings)) Parent-reported emotional function changes (PedsQL-PC (subscale Emotional Functioning)) Self-reported sociability function changes (PedsQL-C (subscale Get Along with Others)) Parent-reported sociability function changes (PedsQL-PC (subscale Emotional Functioning)) Balance changes (Pediatric Balance Scale) Position changes (Sitting Assessment Scale) Proprioception-coordination changes (Developmental Coordination Disorder Questionnaire 2007 (DCDQ'07)) Autonomous nervous system activation function changes (Heart Rate Variability (HRV))
Starting date	12 October 2019
Contact information	Teresa Xipell Prunés, teresa.xipell@eug.es
Notes	Estimated study completion date: September 2020. On 23 June 2020, no full-text publication was available.

APPENDICES

Appendix 1. Search strategy for Central Register of Controlled Trials (CENTRAL)

For **Children** the following thesaurus terms and text words were used:

#1.[mh ^adolescent] or [mh child] or [mh infant]

#2.(infan* or neonat* or newborn or baby or babies or child* or schoolchild* or kid or kids or toddler* or adoles* or teen* or boy* or girl* or minor* or underag* or (under NEXT ag*) or juvenil* or youth* or kindergar* or puber* or pubescen* or prepubescen* or prepuberty* or pediatric* or paediatric* or peadiatric* or school* or preschool* or highschool* or "high school"):ti,ab,kw

#3.(pediatric* or paediatric* or child* or adolesc*):so

#4.#1 or #2 or #3

For **Cancer** the following thesaurus terms and text words were used:

#5.([mh Neoplasms] or (oncolog* or neoplas* or carcinom* or tumor* or tumour* or cancer* or malignan* or "hemato-oncologic*" or hematolo* or "haemato-oncologic*" or haematolo or bone marrow transplant* or leukemi* or leukaemi* or AML or lymphom* or hodgkin* or "T-cell" or "B-cell" or "non-hodgkin" or sarcom* or Ewing* or osteosarcom* orwilms* or nephroblastom* or neuroblastom* or rhabdomyosarcom* or teratom* or hepatom* or hepatoblastom* or medulloblastom* or PNET* or retinoblastom* or meningiom* or gliom*):ti,ab,kw) not (breast*:ti or [mh "breast neoplasms"])

For **Physical therapy** the following thesaurus terms and text words were used:

#6.[mh "Physical Therapy Modalities"] or [mh ^"physical therapy specialty"] or [mh ^"physical and rehabilitation medicine"] or [mh "range of motion, articular"] or [mh ^gait] or [mh ^proprioception]

#7.[mh ^"postural balance"] or [mh ^"muscle stretching exercises"]

#8.[mh "ultrasonic therapy"] or [mh ^Cryotherapy]

#9.[mh ^"short-wave therapy"]

#10.#6 or #7 or #8 or #9

#11.((exercis* NEAR/4 (therap* or strength or balance or gait or stretch*)) or (manual NEXT therap*) or (physical NEXT therap*) or physiotherap* or "stability training" or "muscle training" or "strength training" or "resistance training" or locomotion* or (functional NEXT therap*) or "weight lifting" or kinesiotherap* or manipulation* or "short-wave-therap*" or cryotherap* or electrotherap* or "ultraso* therap*" or (rehab* NEAR/6 physical)):ti,ab,kw

#12.#4 and #5 and #10 and #11

^: denotes a non-exploded subject heading

mh: subject heading

[so]: Word in journal title

[tw]: text word (title and abstract)

near/6: up to 6 words can intervene between the word(s) to the left of the operator and the word(s) to the right.

*=zero or more characters

Appendix 2. Search strategy for MEDLINE Ovid

1 For **Children** the following MeSH headings and text words were used:

1. adolescent/ or exp child/ or exp infant/

2. (infan* or neonat* or newborn or baby or babies or child* or schoolchild* or kid or kids or toddler* or adoles* or teen* or boy* or girl* or minor* or underag* or under ag* or juvenil* or youth* or kindergar* or puber* or pubescen* or prepubescen* or prepuberty* or pediatrics or pediatric* or paediatric* or peadiatric* or school* or preschool* or highschool*).mp.

3. (pediatric* or paediatric* or child* or adolesc*).jw.

4. or/1-3

2 For **Cancer** the following MeSH headings and text words were used:

1. exp Neoplasms/

2. (oncolog* or neoplas* or carcinom* or tumor* or tumour* or cancer* or malignan* or hemato-oncological or hematolo* or bone marrow transplant* or leukemi* or leukaemi* or AML or lymphom* or hodgkin* or T-cell or B-cell or non-hodgkin or sarcom* or Ewing* or osteosarcom* or wilms* or nephroblastom* or neuroblastom* or rhabdomyosarcom* or teratom* or hepatom* or hepatoblastom* or medulloblastom* or PNET* or retinoblastom* or meningiom* or gliom*).mp.

3. 1 or 2

4. breast*.ti. or exp breast neoplasms/

5. 3 not 4

3 For **Physical therapy** the following MeSH headings and text words were used:

1. exp Physical Therapy Modalities/

2. physical therapy specialty/

3. "physical and rehabilitation medicine"/

4. "range of motion, articular"/

5. gait/

6. proprioception/ or postural balance/

7. muscle stretching exercises/

8. short-wave therapy/ or exp ultrasonic therapy/

9. Cryotherapy/

10. ((exercis* adj4 (therapeutic or strength or balance or gait or stretch*)) or manual therap* or physical therap* or physiotherap* or stability training or muscle training or strength training or locomotion* or functional therap* or weight lifting or kinesiotherap* or manipulation* or short-wave-therap* or cryotherap* or electrotherap* or ultraso* therap* or (rehab* adj6 physical)).tw,kf.

11. or/1-10

4 For **RCTs and CCTs** the following MeSH headings and text words were used:

1. exp clinical trial/

2. control groups/

3. double-blind method/

4. random allocation/

5. cross-over studies/

6. (random* or quasi-random* or quasi-experiment* or cross-over or placebo or trial or groups or double blind).mp.

7. randomized controlled trial/

8. or/1-7

Final search: 1 and 2 and 3 and 4

/=MeSH term, *=zero or more characters

adj4, adj6, adj#= up to # words can intervene between the word(s) to the left of the operator and the word(s) to the right

[mp]= multiple places (title, abstract, subject headings, author keywords)

[tw]= text word (title and abstract)

[kf]= author keyword

[jw]= Word in journal title

The child search was based on the CCG standard search strategy for children (Leclercq 2013).

Appendix 3. Search strategy for Embase Ovid

1 For **Children** the following Emtree terms and text words were used:

1. adolescent/ or exp child/ or exp infant/

2. (infan* or neonat* or newborn or baby or babies or child* or schoolchild* or kid or kids or toddler* or adoles* or teen* or boy* or girl* or underag* or under ag* or juvenil* or youth* or kindergar* or puber* or pubescen* or prepubescen* or prepuberty* or pediatrics or pediatric* or paediatric* or peadiatric* or school* or preschool* or highschool*).mp.

3. (pediatric* or paediatric* or child* or adolesc*).jx.

4. or/1-13

2 For **Cancer** the following Emtree terms and text words were used:

1. exp neoplasm/

2. (oncolog* or neoplas* or carcinom* or tumor* or tumour* or cancer* or malignan* or hemato-oncological or hematolo* or bone marrow transplant* or leukemi* or leukaemi* or AML or lymphom* or hodgkin* or T-cell or B-cell or non-hodgkin or sarcom* or Ewing* or osteosarcom* or wilms* or nephroblastom* or neuroblastom* or rhabdomyosarcom* or teratom* or hepatom* or hepatoblastom* or medulloblastom* or PNET* or retinoblastom* or meningiom* or gliom*).mp.

3. 1 or 2

4. breast*.ti. or exp breast tumor/

5. 3 not 4

3 For **Physical therapy** the following Emtree terms and text words were used:

1. exp physiotherapy/

2. physical medicine/ or electrostimulation therapy/ or exp kinesiotherapy/ or exp manipulative medicine/ or exp ultrasound therapy/

3. "range of motion"/

4. gait/

5. proprioception/

6. exp body equilibrium/

7. stretching exercise/

8. exp diathermy/

9. cryotherapy/

10. ((exercis* adj4 (therapeutic or strength or balance or gait or stretch*)) or manual therap* or physical therap* or physiotherap* or stability training or muscle training or strength training or locomotion* or functional therap* or weight lifting or kinesiotherap* or manipulation* or short-wave-therap* or cryotherap* or electrotherap* or ultraso* therap* or (rehab* adj6 physical)).tw,kw.

11. or/6-15

12. adolescent/ or exp child/ or exp infant/

13. (infan* or neonat* or newborn or baby or babies or child* or schoolchild* or kid or kids or toddler* or adoles* or teen* or boy* or girl* or underag* or under ag* or juvenil* or youth* or kindergar* or puber* or pubescen* or prepubescen* or prepuberty* or pediatrics or pediatric* or paediatric* or peadiatric* or school* or preschool* or highschool*).mp.

14. (pediatric* or paediatric* or child* or adolesc*).jx.

15. or/1-14

4 For **RCTs and CCTs** the following Emtree terms and text words were used:

1. exp clinical trial/

2. control groups/

3. double blind procedure/

4. randomization/

5. crossover procedure/

6. (random* or quasi-random* or quasi-experiment* or cross-over or placebo or trial or groups or double blind).mp.

7. randomized controlled trial/

8. or/1-7

Final search 1 and 2 and 3 and 4

/=Emtree term; *=zero or more characters

adj4, adj6, adj#= up to # words can intervene between the word(s) to the left of the operator and the word(s) to the right

[mp]= multiple places (title, abstract, subject headings, author keywords)

[tw]= text word (title and abstract)

[kw]= author keyword

[jx]= Word in journal title

Appendix 4. Search strategy for CINAHL/EBSCO

1 For **Children** the following Subject headings and text words were used:

S1. ((MH "Child+") OR (MH "Adolescence+")) OR (infan* or neonat* or newborn or baby or babies or child* or schoolchild* or kid or kids or toddler* or adoles* or teen* or boy* or girl* or minor* or underag* or under ag* or juvenil* or youth* or kindergar* or puber* or pubescen* or prepubescen* or prepuberty* or pediatrics or pediatric* or paediatric* or peadiatric* or school* or preschool* or highschool*) OR SO (pediatric* or paediatric* or child* or adolesc*)

2 For **Cancer** the following Subject headings and text words will be used:

S1. (MH "Neoplasms+") OR (oncolog* or neoplas* or carcinom* or tumor* or tumour* or cancer* or malignan* or hemato-oncological or hematolo* or bone marrow transplant* or leukemi* or leukaemi* or AML or lymphom* or hodgkin* or T-cell or B-cell or non-hodgkin or sarcom* or Ewing* or osteosarcom* or wilms* or nephroblastom* or neuroblastom* or rhabdomyosarcom* or teratom* or hepatom* or hepatoblastom* or medulloblastom* or PNET* or retinoblastom* or meningiom* or gliom*)

S2. (MH "Breast Neoplasms+") OR TI breast*

S3. S1 NOT S2

3 For **Physical therapy** the following Subject headings and text words were used:

S1. (MH "Physical Therapy+")

S2. (MH "Research, Physical Therapy")

S3. (MH "Proprioception+")

S4. (MH "Balance, Postural")

S5. (MH "Range of Motion")

S6. (exercis* n4 (therapeutic or strength or balance or gait or stretch*)) or manual therap* or physical therap* or physiotherap* or stability training or muscle training or strength training or locomotion* or functional therap* or weight lifting or kinesiotherap* or manipulation* or short-wave-therap* or cryotherap* or electrotherap* or ultraso* therap* or (rehab* n6 physical)

S7. S1 OR S2 OR S3 OR S4 OR S5 OR S6

4 For **RCTs and CCTs** the following MeSH headings and text words were used:

S1. ((MH "Random Sample+") OR (MH "Control Group") OR (MH "Clinical Trials+") OR (MH "Randomized Controlled Trials") OR (MH "Crossover Design") OR (MH "Quasi-Experimental Studies+")) OR (random* or quasi-random* or quasi-experiment* or cross-over or placebo or trial or groups or double blind)

Final search: 1 and 2 and 3 and 4

MH= subject heading TI= title SO= journal title/source

+= denotes that the subject heading was exploded

*= zero or more characters

n4, n6 (n#) = adjacency operator where # is the maximum number of words that two terms can be separated by

Appendix 5. Search strategy for PEDro

Three different search strategies, combining the results with OR were used to search this database:

Search A

1. paediatric* <Abstract & Title> field

2. oncology <Subdiscipline> field

3. stretching, mobilisation, manipulation, massage <Therapy> field.

4. clinical trial <Method> field

Search B

1. child* <Abstract & Title> field

2. oncology <Subdiscipline> field

3. stretching, mobilisation, manipulation, massage <Therapy> field.

4. clinical trial <Method> field

Search C

1. adolescent* <Abstract & Title> field

2. oncology <Subdiscipline> field

3. stretching, mobilisation, manipulation, massage <Therapy> field.

4. clinical trial <Method> field

Appendix 6. Key terms for ongoing trials registries

1. www.isctrn.org **(ISCTRN register)**
We browsed by "Cancer" studies, limited by "Child", and scanned results with the search terms: "physical therapy"; physiotherapy; rehabilitation.

2. www.clinicaltrials.gov **(National Institutes of Health (NIH) Register for ongoing trials)**
We searched at the Advanced search page:
Study type: Interventional studies
Group: Child (birth-17yrs) will be checked
Condition: cancer OR neoplasm OR oncology
Interventions: "physical therapy" OR physiotherapy OR rehab*

3. http://apps.who.int./trialsearch **(WHO portal)**
We will search at the Advanced search page:
(cancer OR oncology OR neoplasm) AND (physical therapy OR physiotherapy OR rehabilitation)
Check box for clinical trials in Children

Appendix 7. Key terms for conference proceedings

ASCO (American Society of Clinical Oncology) website

We searched the meeting library (meetinglibrary.asco.org) with different search strategies combining key words.

Searches separated by semicolons:

"physical therapy" child; "physical therapy" children; "physical therapy" childhood; "physiotherapy" child; "physiotherapy" children; "physiotherapy" childhood; "rehabilitation" child; "rehabilitation" children; "rehabilitation" childhood.

MASCC (Multinational Association for Supportive Care in Cancer) website

We searched the meeting abstracts (http://www.mascc.org/past-annual-meetings) with different key words:

"physical therapy"; physiotherapy; rehabilitation; child; infant

The **SIOP (International Society for Paediatric Oncology)** and **ASPHO (American Society of Pediatric Hematology/Oncology)** abstracts were searched by using the "Find text" in pdf documents with the keywords: physical therapy; physiotherapy; rehabilitation

HISTORY

Protocol first published: Issue 1, 2018

CONTRIBUTIONS OF AUTHORS

Paula A. Ospina, MScPT: responsible for protocol development, database search, screening of articles for inclusion, data extraction, and writing of the final review paper.
Alyssa McComb, MScPT: responsible for protocol development, database search, screening of articles for inclusion, data extraction, and contributing to the writing of the final review.
Lesley Wiart, PT, PhD: responsible for protocol development, interpretation of findings, and review preparation and conclusions.
David Eisenstat, MD, MA, FRCPC: content expert. Responsible for protocol development, interpretation of findings, review preparation and conclusions.
Margaret L. McNeely, PT, PhD: methodological expert. Responsible for protocol development, overseeing the database search, third-party arbitration to reach consensus in disagreements, screening of articles for inclusion, data extraction, interpretation of findings and review conclusions, and writing of the final review paper.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Canadian Child Health Clinician Scientist Training Program (Dr. Wiart), Women and Children's Health Research Institute (Ms. Ospina, Dr. Wiart, Dr. Eisenstat, Dr. McNeely), Stollery Children's Foundation (Dr. Wiart), Alberta Policy Wise for Children and Families (Dr. Wiart), Canada

  Research project support for Dr. Wiart's research projects

External sources

- No sources of support provided

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We identified an omission in the list of secondary outcomes in the protocol. The categories 'functional abilities and mobility' and 'motor development and performance' were not listed. However, some of the tests for these were included under the category of 'balance'. We have revised to include the category of 'motor development and performance', and we added the following tests: Bruininks Osteretsky Test of Motor Proficiency (BOTMP), Bruininks Osteretsky Test of Motor Proficiency Second Edition (BOT-2), Alberta Infant Motor Scale (AIMS), Movement Assessment Battery for Children (Movement ABC-2), Peabody Developmental Motor Scales (PDMS-2), Miller Function and Participation Scales (MFUN-PS), Gross Motor Function Measure (GMFM). In the category of 'functional abilities and mobility', *we* added the following tests: Functional Mobility Assessment (FMA) tool, Timed Up and Down Stairs (TUDS), Timed Up and Go (TUG), Functional Independence Measure for Children (WeeFIM), Pediatric Evaluation of Disability Inventory (PEDI), and Vineland Adaptive Behaviour Scale.

We updated the CENTRAL search strategy with the assistance of the University of Alberta Health Sciences librarian as we identified some minor notation errors that did not allow us to re-run the search strategy. No content was modified; only the order of statements and punctuation were corrected.

INDEX TERMS

Medical Subject Headings (MeSH)

*Exercise; Exercise Therapy; *Neoplasms [therapy]; Physical Fitness; Physical Therapy Modalities; Quality of Life

MeSH check words

Adolescent; Adult; Child; Child, Preschool; Humans; Infant; Infant, Newborn; Young Adult